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Long-Term Physical Training and Left Ventricular Remodeling After Anterior Myocardial Infarction: Results of the Exercise in Anterior Myocardial Infarction (EAMI) Trial

PANTALEO GIANNUZZI, MD, LUIGI TAVAZZI, MD, FACC, FESC, PIER LUIGI TEMPORELLI, MD, UGO CORRÀ, MD, ALESSANDRO IMPARATO, MD, MARINELLA GATTONE, MD, AMERIGO GIORDANO, MD, LUIGI SALA, MD,* CARLO SCHWEIGER, MD,† CLAUDIO MALINVERNI, MD,‡ FOR THE EAMI STUDY GROUP§

Veruno, Monza, Rho and Mozzo, Italy

Objectives. **The aim of this multicenter randomized study was to investigate whether long-term physical training would influence left ventricular remodeling after anterior myocardial infarction.**

Background. **Exercise is currently recommended for patients after myocardial infarction; however, the effects of long-term physical training on ventricular size and remodeling still have to be defined.**

Methods. **Patients with no contraindications to exercise were studied 4 to 8 weeks after anterior Q wave myocardial infarction and 6 months later by echocardiography at rest and bicycle ergometric testing. After the initial study, patients were randomly allocated to a 6-month exercise training program (n = 49) or a control group (n = 46). A computerized system was used to derive echocardiographic variables of ventricular size, function and topography.**

Results. **After 6 months, a significant ($p < 0.01$) increase in work capacity (from 4,596 ± 1,246 to 5,503 ± 1,335 kp-m) was observed only in the training group, whereas global ventricular size, regional dilation and shape distortion did not change in either the control or the training group. However, compared with patients with an ejection fraction >40%, patients with an ejection fraction ≤40% had more significant ($p < 0.001$) ventricular enlargement at entry and demonstrated further ($p < 0.01$) global and regional dilation after 6 months, in both the control and the training group (end-diastolic volume from 77 ± 14 to 85 ± 17 ml/m^2 in the control group and from 74 ± 11 to 77 ± 15 ml/m^2 in the training group; regional dilation from 46 ± 18% to 57 ± 21% in the control group and from 42 ± 18% to 44 ± 26% in the training group). Ventricular size and topography did not change in patients with an ejection fraction >40%.**

Conclusions. **Patients with poor left ventricular function 1 to 2 months after anterior myocardial infarction are prone to further global and regional dilation. Exercise training does not appear to influence this spontaneous deterioration. Thus, postinfarction patients without clinical complications, even those with a large anterior infarction, may benefit from long-term physical training without any additional negative effect on ventricular size and topography.**

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Our understanding of the pathophysiologic importance of left ventricular volume after myocardial infarction has been greatly enhanced by the recognition of the progressive nature of ventricular dilation (1–15), which is more pronounced in anterior than in inferior infarcts (8,10,15) and can profoundly affect ventricular function and prognosis in postinfarction patients (4,16,17). It is also known that several factors may influence and modify the remodeling process, such as infarct size, infarct healing, ventricular wall stress, different loading conditions, medications, continued ischemia and possibly other not yet well defined determinants (6,11–15,18,19). This is the case with physical training.

Exercise training is currently recommended for patients after acute myocardial infarction because of its beneficial effects (20–31). However, Jugdutt et al. (32) recently reported a significant deterioration in both global and regional function after physical training in some patients with anterior infarction. These findings have not yet been confirmed by other observations and to date, no controlled studies on the effects of exercise training on ventricular cavity dimension and remodeling are available. Therefore, the Exercise Training in Anterior Myocardial Infarction (EAMI) trial was designed as a randomized controlled trial (33) to determine whether long-term exercise training would influence ventricular size and remodeling after anterior myocardial infarction. The primary objective was to assess the effects of a long-

From the Department of Cardiology, 'Clinica del Lavoro' Foundation, IRCCS Medical Center of Rehabilitation, Veruno; *San Gerardo Hospital, Monza; †Passirana Hospital, Rho, and ‡Rehabilitation Hospital, Mozzo, Italy. §The investigators and institutions participating in the EAMI trial are listed in the Appendix. The study was supported by the 'Clinica del Lavoro' Foundation, Pavia, Italy.

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Address for correspondence: Dr. Pantaleo Giannuzzi, Divisione di Cardiologia, Centro Medico di Riabilitazione, 28010 Veruno, Italy.

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term exercise training program (lasting 6 months) on global ventricular cavity dimension, function and topography. Secondary aims were to define the role of myocardial ischemia in the possible deterioration of left ventricular function and to investigate the effects of physical training on the autonomic nervous system profile and neuroendocrine activation during exercise. Changes in the hemostatic variables and lipids were also recorded.

Methods

Study protocol and organization. The EAMI trial was a multicenter, randomized, controlled study in patients with recent first anterior Q wave myocardial infarction and no standard contraindications to exercise who were enrolled at four cardiac rehabilitation centers (Appendix) in northern Italy.

All patients underwent functional evaluation both at entry (4 to 8 weeks after the acute episode) and 6 months later (at the end of the study) at the coordinating center located at the Cardiology Department of Veruno Medical Center. The functional evaluation included: 1) physical examination and chest roentgenogram; 2) Doppler echocardiographic study; 3) standard upright exercise stress testing on a bicycle ergometer with first pass radionuclide ventriculography and technetium-99m sestamibi single-photon emission computed tomographic (SPECT) perfusion scan; 4) determination of venous blood lactate concentration and circulating catecholamine serum level at baseline and during exercise testing; and 5) 24-hour ambulatory electrocardiographic (ECG) monitoring for both arrhythmias and heart rate variability analysis. All cardioactive drugs were discontinued before both the initial and the final evaluation: angiotensin-converting enzyme inhibitors 1 week before, beta-adrenergic blocking agents ≥72 h before, calcium antagonists and nitrates 48 h before study. No patients were receiving digitalis or amiodarone. The two-dimensional echocardiogram was repeated at the 2nd month and the ergometric test, together with the clinical examination, at 2-month intervals. In addition, coronary artery angiography was performed during the same 6-month period of the study.

After the initial evaluation, patients were randomly allocated to physical training or a control group. During the study, they were followed up at the participating centers that were responsible for the clinical evaluation and management of the exercise training program. All patients provided signed, informed consent before randomization.

The principal investigator of the study at the coordinating center of Veruno was responsible for the overall execution of the trial. All data were collected and analyzed at the coordinating center. The study had been approved by the local scientific and ethics committees.

Study patients. Consecutive male patients, survivors of a first acute myocardial infarction, in New York Heart Association functional class I or II were admitted into this prospective study if the following criteria were met: 1) history of anterior Q wave acute infarction (4 to 8 weeks previously), supported by a typical history of chest pain, evolutionary ECG changes and new abnormal Q waves (≥30 ms) in at least two adjacent precordial leads and leads I or aVL, a typical pattern of elevated serum myocardial enzymes and persistent left ventricular asynergy on two-dimensional echocardiography; 2) sinus rhythm and no atrioventricular or intraventricular conduction disturbances; 3) no contraindications to exercise training and absence of angina at rest and signs or symptoms of cardiac failure at the time of the initial evaluation; and 4) echocardiographic images of adequate quality for quantitative analysis.

Exclusion criteria were: 1) rest ejection fraction <25%; 2) low work capacity (≤50 W); 3) angina at low level exercise (≤50 W); 4) exertional angina uncontrolled by medical therapy; 5) a high risk exertional scintigraphic pattern as defined by multiple perfusion defects or, for patients with preserved left ventricular function (rest ejection fraction >40%), a decrease in ejection fraction to <35% during exercise; and 6) inability to participate in a long-term trial for any logistic reason.

From January 1990 to February 1992, 132 patients were studied for possible enrollment. Twenty-nine patients were excluded because of severe exertional ischemia as detected by scintigraphic study (n = 17), low rest ejection fraction (n = 5), angina at low level exercise (n = 4), low work capacity (n = 1) and systemic disease (n = 2). The remaining 103 patients were enrolled and, after the initial evaluation, were randomly allocated to a 6-month exercise training program (51 patients) or control (52 patients).

Reinfarction, heart failure, angina at rest, reduction of effort angina threshold, exertional angina uncontrolled by therapy, coronary artery bypass surgery and angioplasty were considered clinical end points and criteria for withdrawing patients from the study.

Ergometric test. The bicycle ergometric test was performed in the upright position, increasing the load by 25 W every 3 min. The ECG was monitored continuously from lead V_5 and recorded on paper from all leads every minute. Sphygmomanometric blood pressure was measured every 3 min. Blood samples for determination of venous lactate concentration were taken at baseline and at the end of each stage during exercise. The criteria for stopping the test have been previously reported (33).

Lactic anaerobic threshold, defined as the point during the test at which a systematic increase in venous lactate concentration occurred (34), was visually detected by two independent observers in blinded fashion.

Two-dimensional echocardiography. *Data acquisition.* All patients underwent a complete Doppler echocardiographic study with adequate visualization of the four cardiac chambers and ventricular walls by using a phased-array scanner (Hewlett-Packard 77020A). Standard views, including parasternal long-axis, short-axis at the papillary muscle level, apical four- and two-chamber and apical long-axis, were videotaped systematically. Furthermore, for detailed

quantitative analysis of left ventricular asynergy, global function and topographic indexes, digital images from each echocardiographic section were acquired simultaneously and stored by using a computerized system developed in the bioengineering laboratory of Veruno Medical Center. The position of the patient and transducer was also noted for use in serial studies.

Quantitative analysis. The computerized system for automatic detection and quantification of regional wall motion, left ventricular function and remodeling using echocardiographic imaging has been previously described (35). Briefly, the system provides: 1) digital acquisition and storage of images with no quality degradation; 2) assistance in the contouring process; 3) automatic detection of wall motion abnormalities and global and regional dilation; and 4) automatic analysis of regional expansion and distortion. To obtain automatic detection and quantification of abnormalities, 30 normal subjects with a mean age of 52 ± 7 years, with no history of cardiovascular disease or diabetes (considered to be normal on the basis of rest and exercise electrocardiography and echocardiography) were studied, and normal ranges of endocardial length, total endocardial surface area, segmental areas and fractional shortening areas and volumes were computed. For comparison, the endocardial length of both asynergic and normally contracting segments was calculated, and indexes of ventricular enlargement and shape distortion were derived in each patient. In particular, to obtain a more comprehensive analysis of both global and regional left ventricular function, the three apical views (four- and two-chamber and apical long-axis) were analyzed. These allowed us to obtain information on ventricular dimensions and function from three different planes and to explore six different ventricular walls from the base to the apex. The endocardial contour of each view was divided by the computer into 23 segments, equal in length, so that the entire ventricular wall was represented by a total of 69 segments. Ventricular wall motion was assessed by using a fixed reference system. Indexes of both global and regional function and topography were derived as the sum of measurements obtained in each section.

For comparison with normal individuals, abnormal wall motion was automatically detected when the fractional shortening area from end-diastole to end-systole of each segment was <2 SD of the mean values in normal subjects. The extent of wall motion abnormalities was then calculated as a percent of the total endocardial length. Global ventricular enlargement and regional dilation were also automatically identified when the total endocardial surface area and segmental areas at the end-diastolic frame exceeded 2 SD of the mean values in normal subjects.

Topographic measurements were derived to provide a more comprehensive understanding of the remodeling process. These included expansion index, regional dilation and regional shape distortion. The expansion index was computed as the ratio of the asynergy-containing endocardial segment length to that of the corresponding segments in normal subjects. The extent of regional dilation was calculated as a percent of the endocardial length of dilated segments to the total endocardial length. Regional shape distortion of dilated segments and of both asynergic and nonasynergic segments was also computed. Distortion was expressed as the ratio of the area difference between dilated, asynergic or nonasynergic segments in the patient and corresponding segments in normal subjects to the corresponding endocardial length in the normal subjects.

Left ventricular ejection fraction was calculated from end-diastolic and end-systolic volumes that were computed from the outlines of two apical views (apical long-axis and four-chamber) using the biplane area-length method (36). All measurements were derived in blinded fashion from three consecutive cardiac cycles and the mean values were used for subsequent analysis. Endocardial surface area and volumes were expressed as a function of body surface area that was estimated at each study.

Training intervention. The exercise training program was worked out in accordance with the rehabilitation centers taking part in the study. The target heart rate was 80% of that achieved at the peak incremental exercise. Initially patients randomized for physical training participated in a supervised, continuous session of 30-min bicycle ergometry at least three times a week for 2 months. Thereafter, they continued the exercise program (30-min bicycle ergometry three times a week) at home reporting to the laboratory every 2 weeks when a new level of exercise could be tested and prescribed so as to maintain the target heart rate for physical training. In addition, patients were asked to take a brisk daily walk for ≥30 min as part of the home-based exercise program. They were instructed to fill in a diary, reporting the date, time, duration and pulse heart rate (self-measured) at the end of each exercise session.

Patients in the control group received educational and psychological support but no formal exercise program, and they were invited to continue their usual lifestyle but to avoid any strenuous physical activity.

Statistical analysis. Because previous data on changes in ventricular volumes during physical training were lacking, no formal sample size was statistically calculated for this study.

Baseline characteristics of the two groups were compared using the chi-square test for discrete variables. All data were analyzed comparing the initial (at entry) with the final (after 6 months) study. Differences between the two groups and changes over time within each group, as well as any interaction (different trends between groups) were assessed by multivariate repeated measures analysis of variance (ANOVA). Differences were considered significant at a p value < 0.05. Results are expressed as mean value ± 1 SD.

Results

A total of 103 men were enrolled in the study and randomly allocated to a 6-month exercise training program

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Table 1. Initial Patient Data

	Control Group (n = 46)	Training Group (n = 49)
Age (yr)	50 ± 8	51 ± 9
Body surface area (m^2)	1.88 ± 0.13	1.89 ± 0.15
History		
Hypertension	8 (17)	15 (31)*
Diabetes	6 (13)	3 (6)
Hypercholesterolemia	22 (48)	26 (53)
Smoking habit	34 (74)	34 (69)
Thrombolytic therapy	35 (76)	32 (65)
Peak creatine kinase (IU/liter)	2,421 ± 983	2,560 ± 1,072
Abnormal Q waves (no.)	4.7 ± 2	4.7 ± 2.1
Cardiothoracic ratio on chest X-ray film	0.47 ± 0.06	0.46 ± 0.04
Exercise-induced reversible perfusion defects	38 (83)	37 (76)
Ejection fraction ≤40%	15 (33)	16 (33)
Multivessel coronary artery disease	10/35 (29)	10/37 (27)
Patency of infarct-related vessel	21/35 (60)	21/37 (57)
Interval since infarction (weeks)	5.2 ± 1	5.4 ± 1.2

*p = 0.04. Data are presented as mean value ± SD or number (%) of patients. Thirty-five patients in the control group and 37 in the training group underwent coronary artery angiography.

(51 patients) or to a control group (52 patients). Six patients (one in the training group and five in the control group) were withdrawn from the study because of unstable angina requiring coronary artery bypass graft surgery, and two patients died (one [in the training group] from sudden death and one [in the control group] from cancer) during the 6-month period of the study. Therefore, 95 patients (mean age 51 ± 8 years) completed the study (that is, they were evaluated both at entry and after 6 months). These patients represent the final study group. Of them, 49 were in the training group and 46 in the control group.

The initial data from the 95 patients who completed the study are reported in Table 1. The clinical data were similar in the two groups; infarct size appeared equivalent and patients with an ejection fraction ≤40%, exercise-induced reversible perfusion defects, multivessel coronary artery disease and patency of the infarct-related vessel were equally distributed in both groups. Furthermore, except for angiotensin-converting enzyme inhibitors, which were more frequently administered in the control group than in the training group, there was no difference between the two groups in the medications received during the 6-month period of the study (Table 2). Medications were also matched in the subgroup with an ejection fraction ≤40%.

Exercise performance (Tables 3 and 4). Heart rate and venous lactate concentration at rest were similar in the two groups both at entry and at the final evaluation. Systolic blood pressure at rest decreased significantly after 6 months only in the training group, but the decrease in rate-pressure product observed in this group was not statistically significant.

Maximal heart rate decreased ($p < 0.01$) in both groups, whereas maximal systolic blood pressure, rate-pressure product and peak venous lactate concentration did not change significantly after 6 months. Initially, total work capacity was similar in the two groups; after 6 months, it did not change in the control group but it increased significantly ($p < 0.001$) by 20% in the training group (from 104 ± 16 to 113 ± 15 W, exercise time from 11 ± 2 to 13 ± 2 min, that is, from 4,596 ± 1,246 to 5,508 ± 1,335 kp-m]). Similarly, lactic anaerobic threshold was significantly delayed (from 46 ± 13 to 60 ± 14 W, $p < 0.01$) only in the training group (Table 3). The improvement in exercise capacity observed in the training group was slightly greater (23%) in patients with an ejection fraction >40% than in those with an ejection fraction ≤40% (18%), but the difference was not statistically significant.

Table 2. Medication During the 6-Month Period of the Study

	Control Group (n = 46)	Training Group (n = 49)
Beta-blockers	32 (70)	38 (78)
Calcium channel antagonists	3 (7)	5 (10)
Nitrates	12 (26)	8 (16)
Angiotensin-converting enzyme inhibitors	13 (28)	5 (10)*
Diuretic drugs	3 (7)	4 (8)
Antiarrhythmic agents	3 (7)	2 (4)
Anticoagulant agents	2 (4)	2 (4)
Antiplatelet agents	44 (96)	47 (96)

*p = 0.047. Data are presented as number (%) of patients.

Comparing the initial with the final study at the same maximal work load (Table 4), heart rate, rate-pressure product and venous lactate concentration did not change in the control group but decreased significantly ($p < 0.01$) in the training group.

Data on left ventricular function and topography (Tables 5, 6 and 7). Initial endocardial surface area, volumes, ejection fraction, wall motion abnormalities and topographic indexes were similar in the two groups. After 6 months, both groups demonstrated a slight increase ($p < 0.01$) in ejection fraction, with a decrease in percent wall motion abnormalities and expansion index; in contrast, global ventricular size (endocardial surface area and volumes), regional dilation and ventricular shape distortion did not change in either the control or the training group (Table 5).

As expected, patients with an ejection fraction ≤40% (a priori defined 40% cut point) had greater endocardial surface area and volumes, more extensive wall motion abnormalities with more pronounced regional dilation, infarct expansion and shape distortion at entry than did patients with an ejection fraction >40% ($p < 0.0001$). Moreover, patients with poor left ventricular function at the initial study showed further ($p < 0.01$) ventricular enlargement with an increase in regional dilation and ventricular shape distortion after 6 months, involving both the asynergic and nonasynergic segments (Table 6). Similar results were also obtained when the study group was analyzed according to the initial ventricular dimensions: Patients with ventricular dilation, compared with those with normal ventricular size at the initial

Table 3. Ergometric Test: Rest and Peak Data

	Control Group (n = 46)		Training Group (n = 49)	
	Pre	Post	Pre	Post
Rest				
Heart rate (beats/min)	71 ± 9	70 ± 13	69 ± 10	68 ± 12
Systolic blood pressure (mm Hg)	123 ± 13	127 ± 20	129 ± 18	125 ± 16*
Rate-pressure product (mm Hg × beats/min × 10^3)	8.7 ± 1.5	8.95 ± 2.3	8.9 ± 1.8	8.5 ± 1.8
Venous lactate concentration (mmol/liter)	1 ± 0.4	1.1 ± 0.4	1.04 ± 0.3	1.04 ± 0.4
Peak				
Heart rate (beats/min)	140 ± 18	132 ± 18	142 ± 18	139 ± 17†
Systolic blood pressure (mm Hg)	172 ± 21	171 ± 24	174 ± 23	177 ± 23
Rate-pressure product (mm Hg × beats/min × 10^3)	24.3 ± 4.7	22.7 ± 5	24.6 ± 3.8	24.5 ± 4.2
Venous lactate concentration (mmol/liter)	3.1 ± 1	3 ± 1.2	3.8 ± 1.5	3.6 ± 1.3
Work capacity (kp-m)	4,362 ± 1,137	4,179 ± 1,198	4,596 ± 1,246	5,508 ± 1,335*
Lactic anaerobic threshold (W)	47 ± 14	50 ± 10	46 ± 13	60 ± 14*

*$p < 0.01$ interaction. †$p < 0.01$ within groups. Data are presented as mean value ± SD. Post = final study (after 6 months). Pre = initial study.

study, demonstrated further ($p < 0.01$) global and regional ventricular enlargement after 6 months.

Changes in both global ventricular size and topography observed in patients with poor left ventricular function and ventricular dilation were similar in both the control and the training group (Table 7). In particular, although patients with a low ejection fraction who underwent exercise training demonstrated a significant decrease in percent wall motion abnormalities, with a slight improvement in ejection fraction compared with findings in the control group, both groups had late ventricular dilation (both global and regional) with a further increase in ventricular shape distortion. In contrast, global ventricular size and topographic variables did not change (or showed a slight improvement) in patients in both groups with an ejection fraction >40% (Tables 6 and 7).

Discussion

During the past decade, increasing emphasis has been placed on the progressive nature of ventricular enlargement, which may continue well after the complete histologic healing of the infarcted region and can profoundly affect ventricular function and survival after myocardial infarction (3,4,6,7,9,10,13–17). Although ventricular dilation is primarily related to the extent and location of the histologic damage (3,9,10,15), other interdependent factors may influence and modify the remodeling process (6,11–14,18,19).

Exercise and left ventricular remodeling. Physical training is currently recommended for patients after acute myocardial infarction, as well as for patients with other cardiac conditions. Several beneficial effects have been demonstrated, even in patients with severely depressed ventricular function and chronic heart failure (20–31). These effects have been attributed to peripheral adaptations that result in greater oxygen extraction in the skeletal muscles. Some studies (20,23,24,26,29) have also suggested the possibility of improving left ventricular function by physical training; however, the available data are limited and often contradictory. Furthermore, the effects of exercise training on ventricular size and remodeling after myocardial infarction are not well established (32,37–41). Experimental data are discordant (37–39) and in a clinical study, Jugdutt et al. (32) reported a significant deterioration in both global and regional function after 12 weeks of an exercise training program starting 15 weeks (as a mean) after the acute episode in a small group of patients with anterior myocardial infarction. This study, however, had some limitations (40): it was carried out on small groups of patients and not designed as a randomized trial; standardization of timing of the exercise training was lacking and the topographic indexes were derived only from the echocardiographic short-axis view. Nevertheless, it had considerable impact on clinical practice, raising a cautionary note that the potential to adversely alter global ventricular size and topography exists in highly

Table 4. Ergometric Test: Same Maximal Work Load

	Control Group (n = 46)		Training Group (n = 49)	
	Pre	Post	Pre	Post
Heart rate (beats/min)	135 ± 17	131 ± 17	139 ± 17	128 ± 18*
Rate-pressure product (mm Hg × beats/min × 10^3)	23 ± 4.3	22.3 ± 4.7	24 ± 3.7	21.5 ± 3.9*
Venous lactate concentration (mmol/liter)	3.0 ± 1.08	2.9 ± 1.1	3.7 ± 1.5	3.0 ± 1.4*

*$p < 0.01$ interaction. Data are presented as mean values ± SD. Abbreviations as in Table 3.

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Table 5. Left Ventricular Function and Topography in the Two Study Groups

	Control Group (n = 46)	Training Group (n = 49)
Endocardial surface area (cm^2/m^2)		
Pre	55 ± 8	53 ± 8
Post	56 ± 10	53 ± 8
End-diastolic volume (ml/m^2)		
Pre	63 ± 16	60 ± 14
Post	66 ± 20	61 ± 16
End-systolic volume (ml/m^2)		
Pre	35 ± 16	31 ± 15
Post	36 ± 20	29 ± 16
Ejection fraction (%)		
Pre	48 ± 13	51 ± 14*
Post	50 ± 16	54 ± 14
% wall motion abnormalities		
Pre	34 ± 15	30 ± 16*
Post	31 ± 20	26 ± 18
Expansion index†		
Pre	1.1 ± 0.12	1.08 ± 0.1*
Post	0.98 ± 0.4	0.98 ± 0.4
% regional dilation		
Pre	23 ± 23	20 ± 20
Post	26 ± 29	20 ± 22
Distortion of dilated segments‡		
Pre	0.58 ± 0.33	0.54 ± 0.31
Post	0.55 ± 0.37	0.46 ± 0.36

*$p < 0.001$ within groups. †Expansion index was computed as the ratio of the asynergy-containing endocardial segment length to that in the corresponding segments in normal subjects. ‡Distortion of dilated segments was expressed as the ratio of area difference between dilated segments in the patient and corresponding segments in normal subjects to the corresponding endocardial length in the normal group. Data are presented as mean value ± SD. See text for further explanations. Abbreviations as in Table 3.

Table 6. Left Ventricular Function and Topography Variables in Patients With Low or Preserved Ejection Fraction

	Ejection Fraction	
	≤40% (n = 31)	>40% (n = 64)
Endocardial surface area (cm^2/m^2)		
Pre	61 ± 6	50 ± 5*†
Post	63 ± 7	50 ± 7
End-diastolic volume (ml/m^2)		
Pre	75 ± 13	55 ± 11*†
Post	80 ± 17	56 ± 12
End-systolic volume (ml/m^2)		
Pre	50 ± 12	24 ± 9*†
Post	52 ± 16	23 ± 10
Ejection fraction (%)		
Pre	35 ± 6	57 ± 9*‡
Post	36 ± 8	60 ± 10
% wall motion abnormalities		
Pre	48 ± 7	24 ± 12*‡
Post	46 ± 10	20 ± 16
Expansion index		
Pre	1.18 ± 0.08	1.05 ± 0.16*†
Post	1.2 ± 0.1	0.9 ± 0.4
% regional dilation		
Pre	44 ± 18	11 ± 14*†
Post	50 ± 24	10 ± 17
Distortion of dilated segments		
Pre	0.76 ± 0.14	0.46 ± 0.34*†
Post	0.79 ± 0.15	0.36 ± 0.35
Distortion of asynergic segments		
Pre	0.50 ± 0.19	0.14 ± 0.2*†
Post	0.57 ± 0.22	0.14 ± 0.2
Distortion of nonasynergic segments		
Pre	0.49 ± 0.23	0.1 ± 0.2*†
Post	0.54 ± 0.31	0.09 ± 0.2

*$p < 0.0001$ between groups. †$p < 0.01$ interaction. ‡$p < 0.01$ within groups. Distortion of asynergic and nonasynergic segments was computed as the ratio of area difference between asynergic or nonasynergic segments in the patients and corresponding segments in normal subjects to the corresponding endocardial length in the normal group. Data presented as mean value ± SD. See text and Table 5 for further explanations. Abbreviations as in Table 3.

selected patients with anterior myocardial infarction (41–43). Further confirmation was obviously needed.

Using a randomized controlled design and a detailed quantitative echocardiographic analysis, we demonstrated in this study that long-term physical training in survivors of a first anterior infarction with no standard contraindications to exercise did not influence spontaneous left ventricular remodeling. Exercise training induced positive results in terms of work capacity and muscle metabolism, even in patients with poor left ventricular function, without any apparent effect on the remodeling process.

Exercise and left ventricular dysfunction. We did not find significant changes in left ventricular size and topographic indexes of regional dilation and shape distortion after 6 months in either the control or the training group. However, patients with a low ejection fraction (≤40%) and ventricular dilation at the time of the initial study (4 to 8 weeks after the acute episode) had more significant ventricular enlargement than those with preserved systolic ventricular function, with increased functional infarct size and more pronounced shape distortion. These patients demonstrated further deterioration after 6 months, and changes in both global ventricular size and topography were directionally similar in the control and training groups. Conversely, ventricular cavity dimension and topography did not change in patients with an ejection fraction >40% and normal ventricular size. Thus, in accordance with previous studies, our data underline the progressive nature of ventricular remodeling after infarction. Patients with poor left ventricular function and ventricular dilation soon after myocardial infarction are prone to further late ventricular enlargement, which occurs in both the asynergic and the normally contracting segments. In addition, the present study suggests that exercise training is not responsible for this increasing deterioration.

In fact, compared with the control group, patients with an ejection fraction ≤40% who underwent exercise training demonstrated less ventricular dilation (although this was not statistically significant) and a significant increase in ejection fraction (from 35% to 39%) (Table 7). This would suggest

Table 7. Left Ventricular Function and Topographic Variables by Study Group in Patients With Low or Preserved Ejection Fraction

	Ejection Fraction ≤40%		Ejection Fraction >40%	
	Control Group (n = 15)	Training Group (n = 16)	Control Group (n = 31)	Training Group (n = 33)
Endocardial surface area (cm^2/m^2)				
Pre	63 ± 6	60 ± 5*	51 ± 7	50 ± 5
Post	65 ± 8	61 ± 6	51 ± 8	50 ± 5
End-diastolic volume (ml/m^2)				
Pre	77 ± 14	74 ± 11*	57 ± 12	54 ± 11
Post	85 ± 17	77 ± 15	58 ± 14	54 ± 10
End-systolic volume (ml/m^2)				
Pre	52 ± 13	48 ± 11†	26 ± 10	22 ± 7*
Post	58 ± 16	47 ± 14	25 ± 12	21 ± 7
Ejection fraction (%)				
Pre	34 ± 5	35 ± 6†	55 ± 9	59 ± 9*
Post	33 ± 8	39 ± 7	58 ± 11	61 ± 9
% wall motion abnormalities				
Pre	48 ± 7	48 ± 7†	27 ± 12	22 ± 12*
Post	50 ± 10	43 ± 9	22 ± 18	18 ± 15
Expansion index				
Pre	1.2 ± 0.09	1.17 ± 0.07	1.07 ± 0.1	1.04 ± 0.2*
Post	1.2 ± 0.09	1.18 ± 0.1	0.9 ± 0.4	0.9 ± 0.4
% regional dilation				
Pre	46 ± 18	42 ± 18*	12 ± 17	9 ± 12
Post	57 ± 21	44 ± 26	14 ± 20	8 ± 13
Distortion of dilated segments				
Pre	0.77 ± 0.14	0.74 ± 0.14*	0.49 ± 0.34	0.44 ± 0.33*
Post	0.83 ± 0.16	0.76 ± 0.14	0.41 ± 0.3	0.31 ± 0.34

*$p < 0.001$ within groups. †$p < 0.01$ interaction. Data are presented as mean value ± SD. See text for further explanations. Abbreviations as in Table 3.

that in patients with left ventricular dysfunction, exercise training may even lessen the deterioration in left ventricular size, shape and function over time. However, the number of patients with a low ejection fraction in this study is too limited and the results do not have enough statistical significance to fully substantiate this conclusion.

Long-term physical training inducing a significant decrease in submaximal rate-pressure product may well exert a favorable control on ventricular wall stress and ultimately compensate for the transient increase in wall stress that occurs during the single exercise session. This probably explains why we did not observe any additional negative effects of physical training on ventricular remodeling.

Our patient groups were well matched in terms of baseline clinical characteristics, residual exertional ischemia, ventricular volumes and medications during the 6-month period of the study. The echocardiographic method used was based on a careful standardization of recording and measurement techniques that have been developed and extensively verified in our laboratory (33,35). Except for beta-adrenergic blocking agents, few patients received drugs, such as angiotensin-converting enzyme inhibitors, nitrates and other vasodilators, potentially interfering with the remodeling process. Most of the patients received beta-blockers as a common policy of treatment in the postinfarction period, and they were equally distributed in the training and control groups. Furthermore, patients with standard contraindications to exercise (spontaneous ischemia, signs or symptoms of heart failure, severe exertional ischemia) were carefully screened out. Patients with a very low ejection fraction (<25%) were also excluded because of the possible clinical instability of such patients soon after the acute episode. Therefore, the results of this study may well be applied to all postinfarction patients without clinical complications.

Clinical implications. This study confirms that changes in left ventricular size and topography are progressive after myocardial infarction. Patients with both global and regional dilation and poor left ventricular function 4 to 8 weeks after anterior myocardial infarction are prone to further ventricular enlargement that involves both the asynergic and nonasynergic zones. Exercise training does not appear to influence this spontaneous deterioration. Therefore, postinfarction patients, without clinical complications even those with a large anterior infarction or evidence of moderate residual myocardial ischemia, may benefit from a long-term exercise training program without any additional deterioration of ventricular volumes and topography. Nevertheless, because patients with a low ejection fraction in the present study represent only 33% of the total study group, larger clinical trials are required to confirm these results in this subset of patients.

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Appendix

The EAMI Study Group

The following investigators and Institutions participated in the Exercise Training in Anterior Myocardial Infarction (EAMI) trial*:

Steering Committee: Pantaleo Giannuzzi, MD (Study Chairman); Amerigo Giordano, MD; Luigi Tavazzi, MD.

Coordinating Center: *Clinica del Lavoro Foundation, Medical Center of Rehabilitation—Cardiology Department, Veruno.* Pantaleo Giannuzzi, MD (Study Chairman); Pier Luigi Temporelli, MD; Marinella Gattone, MD; Ugo Corrà, MD; Pedro Silva, MD.

Participating Centers: *San Gerardo Hospital, Cardiology Department, Monza.* Luigi Sala, MD†; Franco Valagussa, MD; Domenico Ravesi, MD; Virgilio Colombo, MD.

Passirana—Rho Hospital—Cardiology Department, Rho. Carlo Schweigher, MD†; Franco Rusconi MD; Donata Castelli, MD; Michaela Palvarini, MD; Stefano Aglieri, MD.

Ospedali Riuniti Di Bergamo—Rehabilitation Hospital, Mozzo. Claudio Malinverni, MD‡; Dante Mazzoleni, MD; Angelo Casari, MD; Orazio Valsecchi, MD.

The Central Laboratories and staff members participating in the study are as follows:

Echocardiography Laboratory: *Medical Center of Rehabilitation, Veruno.* Pantaleo Giannuzzi, MD†; Alessandro Imparato, MD; Pier Luigi Temporelli, MD.

Exercise Metabolic Laboratory: *Medical Center of Rehabilitation, Veruno.* Ugo Corrà, MD†; Santino Magnaghi, MD, Marinella Gattone, MD; Pier Luigi Temporelli, MD.

Radionuclide Laboratory: *Medical Center of Rehabilitation, Veruno.* Riccardo Campini, MD*; Raffaele Giubbini, MD; Michele Galli, MD; Claudio Marcassa, MD; Orazio Zoccarato, PhD.

Autonomic Nervous System Laboratory: *Medical Center of Rehabilitation, Veruno.* Giorgio Mazzuero, MD†; Paola Lanfranchi, MD.

Neurohumoral Laboratory: *University of Milan, Clinica Medica II—Centro Fisiologia Clinica ed Ipertensione, Milan.* Gianni Bolla, MD†; Gastone Leonetti, MD.

Haemostasis Laboratory: *University of Milan, Clinica Medica I, Milan.* Carla Boschetti, MD*; Michele Cortellaro, MD; Patrizia Leonardi, MD.

Bioengineering Laboratory: *Medical Center of Rehabilitation, Veruno.* Giuseppe Minuco, PhD†; Andrea Giordano, PhD; Roberto Colombo, PhD; Fabio Comazzi (Programmer).

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*All institutions are in Italy.
†Principal investigators.

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